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Expression of p53 Protein and Prognosis in Gastric Carcinoma

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A study was carried out to assess whether p53 expression is related to tumour type, grade or pathological characteristics, or to prognosis, in gastric cancer. Immunohistochemical studies were performed to detect p53 protein in sections from 55 consecutive gastrectomy or partial gastrectomy specimens. Tumours were classified for T-stage, histopathological grade and pathological characteristics. Immunohistochemical staining detected p53 protein in 11 (19%) of the 55 specimens. There was no statistically significant difference between patients with p53 positively staining tumours and patients with p53 negatively staining tumours with regard to tumour grade, stage or pathological characteristics (lymph-node infiltration, depth of invasion, necrosis, or necrosis of vessels). Survival time was statistically significantly lower in patients with positively staining tumours (mean survival times 12.0 and 23.4 months, respectively). These results suggest that expression of p53 protein is related to poor prognosis in gastric carcinoma.

KEY WORDS: p53 Protein; Gastric carcinoma; Clinicopathological features; Prognosis

Introduction

p53 is the most commonly mutated gene in human cancer. The high prevalence of p53 mutations in human cancer suggests that p53 could be used as a marker in malignancy. The p53 tumour suppressor gene controls cellular growth after DNA damage through mechanisms involving growth arrest and apoptosis.[1] p53 mutations may occur as early or late events in tumour progression, depending on tissue type. Alterations of the p53 tumour suppressor gene result in defective cellular responses after DNA

damage and dysregulated growth, tumour formation and progression, and potential resistance of tumour cells to certain chemotherapeutic agents.[2] p53 mutations have been found in advanced stages of various tumour types including gastrointestinal cancers.[3,4] A variety of tumours involving mutant p53 have a worse prognosis than tumours of the same type containing no p53 mutations.[5-9] p53 mutations have been associated with aggressive behaviour of various tumour types, including gastric cancers. Abnormal expression of the p53 gene has been shown in gastric cancer tissues and has been related to prognosis with different results. The aim of this study was to investigate whether p53 expression was related to tumour type, grade, pathological characteristics or prognosis in gastric cancer in our hospital where the prevalence of gastric cancer is quite high.

MATERIALS AND METHODS

SPECIMENS

A total of 55 consecutive patients (32 men and 23 women; mean age 55 years ± SE; range, 20 – 80 years) with advanced gastric carcinoma underwent surgery between 1994 and 1998 in the Department of General Surgery, Medical School of Uludağ University. The tumours were classified for T-stage, histopathological grade and pathological characteristics. None of the patients had received preoperative adjuvant therapy. All 55 tumours had invaded the gastric serosa.

DETECTION OF p53

p53 has been detected by immunohistochemical staining of tumour tissue with anti-p53 antibodies,[10] and so we performed immunohistochemical studies for p53 protein on the 55 gastric specimens. All specimens were fixed in 10% formalin and embedded in paraffin. Five representative blocks were selected and serial 5-µm sections were examined by immunohistochemistry. Monoclonal antibodies, specific for p53 protein, were obtained from DAKO. Immunohistochemical staining was performed using the avidin–biotin–peroxidase complex, using monoclonal antibodies. To obtain valid immunohistochemical findings, appropriate control slides (exposed to monoclonal antibodies) of gastric carcinoma were stained at the same time. The immunostained slides were examined independently by two pathologists.

STATISTICAL ANALYSIS

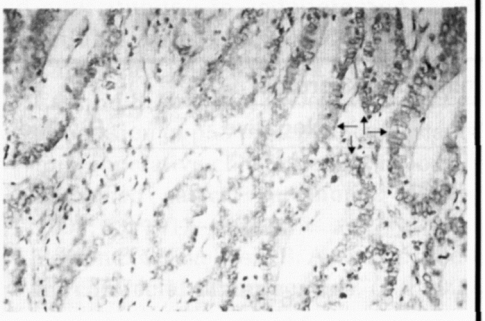
Differences between positively and negatively immunostaining groups with regard to clinicopathological parameters were analysed statistically by the Mann–Whitney *U*-test. Survival data were available for all 55 patients. Corrected survival rates were used (only deaths caused by gastric carcinoma were taken). The probability of survival was calculated using the Kaplan-Meier method, and the significance of the difference between pairs of Kaplan-Meier curves was calculated using the Wilcoxon (Gehan) test. *P*-values < 0.05 were considered to be statistically significant.

RESULTS

Of the 55 tumour specimens, 11 (19%) stained positively for p53 protein (Fig. 1). There was no significant relationship between positive or negative staining and tumour grade, stage or pathological characteristics (lymph-node infiltration, depth of tumour invasion, necrosis or invasion of vessels). The expression of p53 protein in the tumour sections and clinicopathological characteristics of patients with gastric cancer are shown in Table 1.

We did find a statistically significant difference ($P < 0.05$) in survival rates between

FIGURE 1



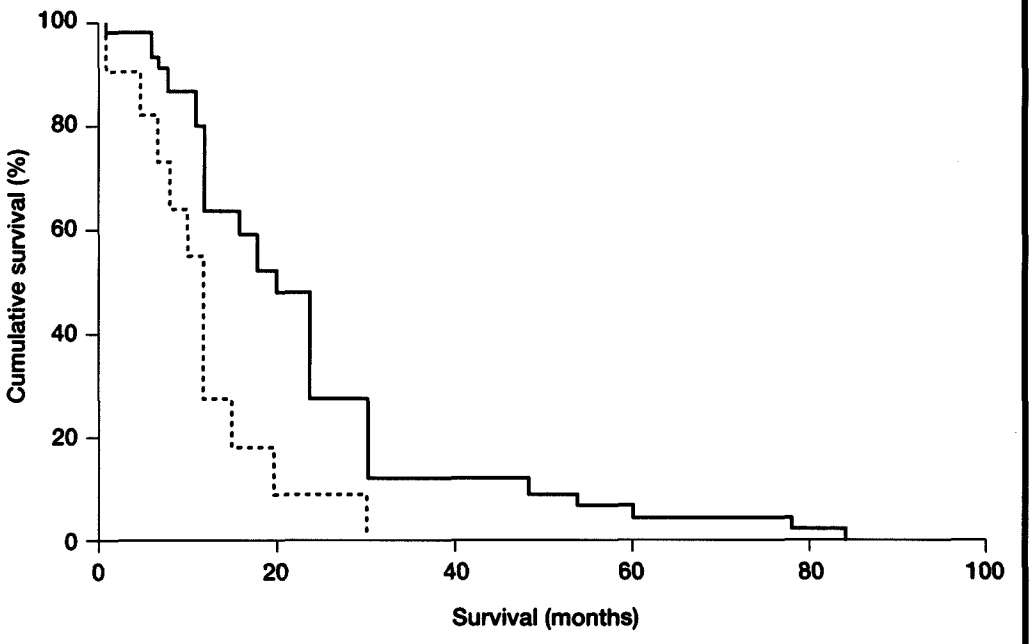
Immunohistochemical staining of p53 protein (arrowed examples) in a section of gastric carcinoma (original magnification x 200).

patients with p53-positive and p53-negative tumours (P = 0.0148). Survival curves of patients with gastric tumours with positive and negative p53 staining are shown in Fig. 2. Mean survival time was 12.0 months in patients with p53-positive tumours; in patients with p53-negative tumours it was longer (23.4 months).

Discussion

The tumour stage and grade of differentiation at diagnosis in gastric carcinoma are considered to be prognostic indicators.[11] Several investigations have shown the expression of p53 protein at different rates in gastric carcinomas,[8] and most of these studies have found positive correlation

FIGURE 2



Kaplan-Meier plot for cumulative survival in 55 patients with gastric carcinoma, comparing p53-negative (—, n = 44) and p53-positive (---, n = 11) tumours.

TABLE 1

Expression of p53 protein and clinicopathological characteristics of patients who had undergone gastrectomy for gastric carcinoma

Clinicopathological characteristic	Staining for p53 protein		*P*-value[a]
	Positive	Negative	
Gender (no. of patients)			NS
Female	4	19	
Male	7	25	
Age (years)			NS
Mean ± SE	56.9 ± 3.4	54.6 ± 2.0	
Range	36 – 80	20 – 78	
Tumour stage (no. of patients)			NS
I	–	6 (4%)	
II	5 (46%)	18 (41%)	
III	6 (54%)	20 (46%)	
Depth of tumour (no. of patients)			NS
T2	2 (18%)	7 (18%)	
T3	9 (82%)	37 (82%)	
Pathological type (no. of patients)			NS
Adenocarcinoma	9	33	
Signet-ring-cell carcinoma	2	11	
Mean ± SEM survival time	12.0 ± 2.4	23.4 ± 2.6	0.0148

[a]Difference between the positively and negatively staining groups (Mann–Whitney *U*-test for clinicopathological factors; Wilcoxon test for the survival data). NS, not significant.

between p53-positive expression and poor prognosis.[7] This can be related to the fact that tumours with p53 protein expression generally occur in advanced gastric carcinomas. In our study, we selected 55 patients with gastric carcinoma at different stages, but all with serosal invasion, to investigate the relationship between the expression of p53 protein and patient prognosis, tumour stage, and clinicopathological characteristics of disease. The statistically significant ($P = 0.0148$) lower survival that we found for patients with p53 protein expression may be associated with advanced gastric carcinomas, which are thought to contain excessive amounts of p53 protein.

Our results indicate that p53 protein expression is related to poor prognosis in patients with gastric carcinoma and, therefore, the investigation of p53 protein expression could provide useful knowledge about predicted postoperative survival. Such information could help the planning of a postoperative treatment strategy.

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